

**APPENDIX 6**

## Preservation of the Threatened Pregnancy with Particular Reference to the Use of Diethylstilbestrol\*

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### HISTORICAL BACKGROUND

**A**BORTION—Premature labor and similar accidents of pregnancy constitute an important problem in the U.S. A survey in 1940 showed that there were about 240,000 noninduced abortions in the United States each year.<sup>1</sup> Rutherford believes that 15 per cent of human pregnancies terminate in spontaneous or induced abortion.<sup>2</sup> The dissatisfaction with existing methods of treatment has been expressed in the constant search for more effective methods. Although many kinds of treatment have been used for the prevention of abortions, certain broad patterns or principal schools of therapy have been noteworthy:

TABLE I

- I. Conservative School
  - Bed rest
  - Sedation
- II. Vitamin School
  - Principally vitamin E
- III. Endocrine School
  - A. Thyroid
  - B. Steroid
  - Progestogens
  - Progestogens and estrogens
  - Estrogens alone

It has been understood for some time that all abortions are not preventable—certainly not those in which the fetus is imperfect or missing (the so-called blighted ovum). Animal breeders have long predicated an inevitable percentage stock loss, and it seems that humans must do likewise. In a study of rejected pregnancies Hertig found 46 per cent pathological fetuses.<sup>3</sup> Mall<sup>4</sup> and Streeter<sup>5</sup> found 89 per cent or about eight in nine normal embryos in abortions occurring at the end of the third month, 50 per cent at the end of the second month, while only 20 per cent were normal at the end of first month. In the last half of a pregnancy, miscarriages because of defective ova are rare.<sup>6</sup> It ap-

pears at this point in our imperfect knowledge of the controlling mechanism, that nature prevails and the majority of imperfect ova are rejected before term. The fact that women who have conceived following a period of sterility abort more frequently than those who conceive readily has long been noted by many observers. Most clinicians agree that such women should be given special treatment in an attempt to prevent abortion.<sup>6</sup> Sperm defects in the husband bear a definite causal relationship to abortions. Preconceptional therapy for both husband and wife, a new concept in the prevention of abortions, will undoubtedly prove to have great value.

The previously mentioned schools of therapy may be described in the following manner.

#### CONSERVATIVE SCHOOL—REST AND SEDATION

This form of treatment embodies the broad principle that restriction of physical activity by enforced rest and a lowering of the body metabolism by sedation will aid in the cessation of the cramps or bleeding accompanying the threatened loss of the pregnancy. Employing this method are those doctors postulating a "fatalistic outcome." They explain to their patients that if the pregnancy and the maternal environment are normal enough, then the body being placed at rest, nature will be kind and the pregnancy continue, but if the pregnancy is sufficiently abnormal or damaged, then no power on earth can save it and to try any other treatment is useless.

The most accepted drugs used for sedation have been the barbiturates. Morphine still enjoys wide use despite some work to show that it increases uterine tone.<sup>7-9</sup>

There can be little doubt that many abuses occur under this method of therapy. Many women have spent the entire pregnancy in bed and willing as they were to do it, have suffered psychological damage. Much worse have been the cases wherein women have been kept in bed for weeks or even months with nothing in the uterus except a few scraps of tissue. The hesitancy of the obstetrician to perform a pelvic examination for fear of disturbing the pregnancy has led to serious errors.

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Diddle, Jack and Pierce recently studied 1,058 obstetrical patients and noted that travel, regardless of distance, means of travel or period of pregnancy had no effect on the abortion rate.<sup>10</sup> This would seem to minimize the value of rest in preventing abortions.

## VITAMIN SCHOOL.

In 1922 an antisterility factor was found in rats and came to be known as vitamin E.<sup>11</sup> It had been noted in the pregnant rat that absence of adequate amounts of vitamin E resulted in a retardation of the establishment of fetal-placental blood vessel development.<sup>12,13</sup> This phenomenon, however, has not been noted in the pregnant woman.<sup>12</sup> It was soon discovered that wheat germ oil was rich in this vitamin and reports on its use in the treatment of threatened and habitual abortion appeared in the literature.<sup>14,15,16</sup> The most frequently appearing names in connection with this therapy have been those of Evan Shute<sup>14</sup> and Vogt-Moller.<sup>15</sup> More recently vitamin E therapy, simplified by the availability of synthetic alphatocopherols in tablet form, has gained wide-spread popularity as an adjuvant in the treatment of threatened and habitual abortions.<sup>17</sup> A few enthusiastic followers, using it as the principal drug in their armamentarium, have reported successful results in as high as 80 per cent of treated patients.<sup>18</sup> However, there is no real agreement as to its value and the prevailing thought has been to minimize its possible worth.

Vitamin C has been declared to be of great value in the maintenance of pregnancy. Vogt was able to produce a high abortion rate in guinea pigs fed a deficient vitamin C diet.<sup>19</sup> Vitamin K deficient levels have been observed in 72 of 79 patients with threatened abortion.<sup>20</sup>

## ENDOCRINE SCHOOL

A. *Thyroid*. It has been known for some time that thyroid deficiency may cause infertility or abortion.<sup>21</sup> Thyroid has gained a highly regarded position in the role of endocrine sheltering of the pregnancy so that most obstetricians today use it as an adjuvant in the treatment of threatened abortion. In our series thyroid in doses of one-half to one grain daily were given to nearly every patient.

B. *Steroid-Progestogens.* This school of therapy began about 1932 when the first potent progestrone became available, has enjoyed widespread popularity and is today the most accepted method of treatment. The work of Reynolds and W. Allen,<sup>22</sup> Falls, Krohn and Lackner<sup>23</sup> and others demonstrated, by means of the intrauterine balloon, the relaxing effect of progestogen on the uterine muscle. The advent of an orally active progestrone tablet, anhydro-oxy-progesterone, simplified

progesterone administration for the physician. Krohn and Harris, in 1941, reported 50 patients with threatened and habitual abortion treated with this drug with 84 per cent success.<sup>24</sup>

The results of progesterone therapy are open to considerable debate. Published statistics have varied from 18.2 per cent success reported by Silbernagel and Burt<sup>17</sup> to above 90 per cent success, reported by Falls and his co-workers.<sup>21</sup> It is notable that the preparation the latter workers used, an aqueous lutein solution, had formerly been believed to be inert. Campbell and Sevringshaus<sup>22</sup> were not very encouraging in their report on the use of progesterone in abortion, and Page and Woods<sup>23</sup> could observe no differences in the carrying rate between women with threatened abortion treated with anhydro-oxy-progesterone and those treated only by bed rest. The wide divergencies between these most favorable and most unfavorable reports from use of the same drug, must demonstrate human fallibility as concerns clinical observation and points out that the true value of progesterone therapy in the treatment of threatened and habitual abortion is still not clearly determined.

**C. Steroid-Progestogens and Estrogens.** It has long been suspected that a lack of progesterone in early pregnancy is probably accompanied by a corresponding lack of estrogenic hormone. The Smiths write categorically "we have yet to find a situation associated with progesterone deficiency in which the estrogens are not also below par."<sup>21</sup> Much experimental work concerning the endocrinology of abortion fills the obstetrical and gynecological literature, with the names of Hamblen,<sup>22</sup> Venning and Browne<sup>23</sup> predominating.

Hamblen pointed out that some observers, including himself, had noted a fall in the pregnandiol titer following the administration of progesterone.<sup>29-31</sup> This fall was interpreted as being due to a suppression of the intrinsic metabolism of progesterone. Hamblen then used both estrogen (in the form of estriol glucuronide) and progesterone and noted that the concomitant administration of these two drugs prevented the depression of the pregnandiol level and at times resulted in a rise.<sup>32</sup> This significant point was utilized by many forward looking obstetricians who began to administer both hormones in the treatment of threatened abortion. In October, 1945, when the paper of Vaux and Rakoff<sup>33</sup> appeared, this treatment received a new stimulation. These observers studied 24 pregnancies in women with a pathological obstetrical background and salvaged 16 pregnancies, a rate of success of approximately 67 per cent. This is a better rate than they had been able to obtain with progesterone alone. Further observations by these observers<sup>33-34</sup> confirmed their be-

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lief that both estrogen and progesterone are necessary in the treatment of habitual abortion.

Hunt<sup>11</sup> recommends progesterone in dosages of 2 to 10 mg. every day and diethylstilbestrol, 1 to 10 mg., daily employing usually the lower range of this dosage. Kurzrok<sup>16</sup> uses natural estrogens in relatively small dosages in pregnant women when there has been a history of genital hypoplasia, and in those cases showing evidence of progesterone lack he uses both estrogens and progesterone. Many obstetricians today administer estrogens along with progestogens and believe their results are better. However, the work of Karnaky, G. V. Smith, O. W. Smith, and P. White would tend to show that the dosages employed by the advocates of the estrogen plus progestogen school of therapy are too small to affect any changes in the hormonal balance during pregnancy.

*D. Steroid-Estrogens Alone.* This school of therapy which advocates the use of large doses of estrogens alone in the treatment of threatened and habitual abortion should be considered as beginning in September, 1942, when the paper by Karnaky was published.<sup>17</sup> This paper pointed out that pregnant women could be administered as much as 200 mg. of diethylstilbestrol daily with no adverse symptoms and, in the opinion of the author, with good results in the treatment of threatened abortion. In habitual abortion Karnaky administered diethylstilbestrol orally, 10 mg., twice daily, while in threatened abortion in the presence of cramps or bleeding he administered 25 to 200 mg. in oil by direct injection into the anterior lip of the cervix. He claimed that this treatment stopped the cramps and bleeding and that many of these patients continued to term. However, Karnaky published no figures to support his contention that the salvage rate was improved by this treatment. Neither did he offer any explanation as to why the drug should be injected into the cervix.

Karnaky believed that diethylstilbestrol in threatened or habitual abortion apparently works by: (1) raising the estrogenic blood level above the estrogenic labor level; (2) keeping the sodium, calcium, potassium, magnesium and phosphorus ions from being concentrated at the level at which uterine contractions are produced; (3) possibly stimulating the corpus luteum to produce more progesterone.

This last conclusion Karnaky based on the work of Heckel and Allen<sup>18</sup> in which they showed that the injection of estrogen in rabbits prevented the regression of the corpus luteum and that the corpora so caused to persist by the injection of estrogens were functional. Diethylstilbestrol had also been

found to cause a pronounced enlargement of follicles and corpora lutea when administered to hypophysectomized rats.<sup>19</sup>

Karnaky's paper was certainly met with a great deal of skepticism. Up to that point large doses of estrogens had enjoyed the rather dubious honor of being able to produce abortion. This concept was based on the work of Parkes,<sup>40</sup> Kelly<sup>41</sup> and Zondek<sup>42</sup> who were able to produce abortions in animals with excessive doses of estrogens. The inability of diethylstilbestrol to perform this function in human females has been amply proved by Abarbanel<sup>43</sup> who administered 2,500 mg. daily for two days to a patient in early pregnancy without noting any disturbances. To another such patient he administered 10,000 mg. in 20 days with no harmful effects. Karnaky<sup>44</sup> treated 35 pregnant women with total dosages of diethylstilbestrol ranging between 789 to 24,050 mg. In no instance was pregnancy interrupted during the administration or following withdrawal of the drug.

The use of diethylstilbestrol was soon sidetracked from threatened abortion to use in the treatment of preeclampsia and in diabetes complicating pregnancy. By long and careful work Smith and Smith showed that preeclamptic toxemias of pregnancy may be associated with an imbalance in the relationship between chorionic gonadotropins on the one hand and estrogen and progesterone levels on the other.<sup>45-47</sup> They found that an abnormally high level of gonadotropins and an abnormally low one of estrogen and progesterone precedes the development of toxemia by some weeks. This prompted them to administer estrogen and progesterone in the treatment of toxemias of pregnancy in an attempt to create a proper balance and in many instances this treatment was said to result in an amelioration of the disease process.<sup>47-49</sup> The Smiths have proposed the concept that withdrawal from the tissues of adequate endocrine support as occurs just prior to menstruation, before threatened abortion, in toxemias of pregnancy, and at the onset of normal labor results in a Goldblatt type of phenomenon due to inadequate vascularization of tissues and the release into the general circulation of a vascular toxin.<sup>50,51</sup> This concept has become known as the "Smith Endocrine Hypothesis."

Because of the high incidence of preeclampsia in diabetes the Smiths were joined in their work by White of the Joslin Clinic. Studies revealed that diabetic gravidae who did not develop abnormal endocrine levels did not often develop toxemia, while a very high percentage of those patients showing a drop in estrogens and progesterone did develop toxemia.<sup>52</sup> By the administration of

diethylstilbestrol in dosage of 40 to 120 mg. daily and pregnenolone 10 to 40 mg. per cent daily, an adjustment in level was obtained and accidents of late pregnancy were minimized.

In March, 1946, the Smiths wrote<sup>11</sup> "we now have evidence that the abnormalities in the production and metabolism of steroid sex hormones may have their incipency in the second trimester, indicating that truly preventive measures should be started beginning about the sixteenth to eighteenth week."

From their studies they concluded: (1) that progesterone facilitates the metabolic conversion of the estrogens and hence depresses their rate of inactivation; (2) that estrogen oxidation inactivation products play an important role in the stimulation of sex steroid secretions; (3) that the production of progesterone around the thirty-eighth week of normal pregnancy is sufficient to reduce estrogen inactivation to such an extent so as to remove the stimulation to steroid hormone production.

The Smiths felt that diethylstilbestrol being inexpensive and active by mouth, might be a valuable drug to forestall accidents of late pregnancy due to insufficient sex steroid production. They believe that large quantities of inactivation, oxidation products of stilbestrol stimulate the production of progesterone. The mechanism by which stilbestrol causes the increased output of progesterone is apparently by a direct effect upon the syncytial cell of the trophoblast, causing the utilization of chorionic gonadotropin in the manufacture of estrogens and progestogens. It must be remembered that in pregnancy the placenta becomes the "pituitary of pregnancy." Accordingly, on administration of adequate doses of diethylstilbestrol, the level of chorionic gonadotropin diminishes<sup>12</sup> while the level of both progesterone and estrogen rises. It can be seen in the light of this that if the trophoblastic cells because of degeneration or atrophy are grossly insufficient, not enough steroid production can be stimulated even with diethylstilbestrol, and the pregnancy cannot continue.

The Smiths studied the urinary pregnandiol output in a pregnant diabetic woman and noted the steady rise in the pregnandiol level during the administration of diethylstilbestrol and a precipitous fall each of three times that the drug was omitted.<sup>13</sup> The fact that there are fluctuations in the pregnandiol levels in normal pregnancy can hardly rule against the action of the drug in this case because no falls in pregnandiol level were noted

while the patient received diethylstilbestrol and a drop occurred each time the drug was stopped, demonstrating fairly conclusively that in this case diethylstilbestrol was responsible for the steady rise in titers of pregnandiol excretion. On the basis of their studies the Smiths advise that in order to prevent late pregnancy accidents, diethylstilbestrol be started at the sixteenth week of pregnancy with 30 mg. daily and increased 5 mg. daily each week through the thirty-fifth week. In their studies and in ours, 25 mg. tablets have been made available to the patients, and the correct dosage obtained by supplementing with 5 mg. tablets.<sup>14</sup>

Although they presented no statistics in favor of the use of diethylstilbestrol in the prevention of accidents of early pregnancy,<sup>15</sup> the Smiths also suggested the administration of diethylstilbestrol, 5 mg. daily, starting at the seventh week of the pregnancy with 5 mg. increase at two week intervals to the sixteenth week and weekly increases thereafter. In their article is reported the fact that Haman performed liver function tests throughout therapy for six weeks postpartum on a woman treated by the diethylstilbestrol regime. There was no evidence of liver damage. The rise in urinary pregnandiol levels as previously noted was confirmed by him. Many other observers have also studied liver function during diethylstilbestrol administration and reported no demonstrable liver damage.<sup>14-17</sup>

With this background as our guide we began the study of the use of diethylstilbestrol in the treatment of threatened and habitual abortion.

#### METHOD OF STUDY

Ninety-six cases of threatened abortion, habitual abortion or threatened premature labor were studied. All of these patients were under our private care and are unselected in any manner.

The following criteria were applied. (1) Threatened abortion was diagnosed by the presence in early pregnancy of bleeding, spotting or staining of blood from the vagina, with or without the presence of cramps. (2) Habitual abortion was defined as the existence of three or more previous spontaneous abortions. (3) Threatened premature labor was defined as the presence in late pregnancy of painful uterine contractions, alarming enough to suspect the probable onset of labor unless treatment was applied.

Our routine of prenatal care was in no way changed. At the onset of symptoms of threatened abortion the patient was ordered to bed and

<sup>11</sup>This must be the reason for the frequent false negative Friedman tests on patients with early pregnancy during stilbestrol administration

<sup>12</sup>The 25 mg. tablets were made available through the courtesy of E. R. Squibb and Sons.

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given per mouth 5 to 25 mg. of diethylstilbestrol at the first dose. Thereafter the dosage was usually 5 mg. three times daily, but so long as symptoms existed 25 mg. every hour was given so that some patients received as much as 200 mg. within 24 hours. As soon as cramps and bleeding were controlled the dosage was gradually dropped to 5 mg. three times a day. As soon as bleeding was not evident for 48 hours the patients were allowed out of bed. The duration of the administration of the drug varied a good deal in

breasts and darkening of the areolae of the nipples and pigmentation of the linea nigra were common. The same pigmentation of these areas was noted in many of the babies, showing that they too shared in the effect of the diethylstilbestrol. This finding in both mothers and babies was transitory and apparently without harm. All babies in this series were normal, with the exception of one baby with multiple deformities of the extremities and spinal column who was born at seven months and survived for a few minutes only.

TABLE II

	STILBESTROL			PROGESTOGENS*						
	No.	Carried	Aborted	No.	Carried	Aborted				
Threatened Abortion	81	71	86.6%	11	13.4%	86	56	65.1%	30	34.9%
Habitual Abortion	10	5	50%	5	50%	7	2	28.6%	5	71.4%
Threatened Premature Labor	4	3	75%	1	25%	1	0	0	1	100%

\*These figures represent the results of 94 consecutive patients just prior to our stilbestrol series. Their treatment was conventional: progestogens (pranone or progesterone)

patients just prior to our stilbestrol series. Their treatment and bed rest.

this group of patients. At first we continued the drug to 36 weeks of pregnancy, fearful that earlier cessation might be harmful. Later we felt that the placenta must be well developed and functioning in the normal cases by the twentieth week of gestation and we thereupon stopped the stilbestrol at about this point. The usual sedative administered to this group of patients were the barbiturates.

In the treatment of threatened premature labor 25 mg. was administered as the first dose of drug and was repeated every hour until contractions ceased. Diethylstilbestrol was then continued at 5 mg. three times a day up to 36 weeks.

Habitual abortion was treated by the administration, beginning in early pregnancy, of stilbestrol 5 mg. three times a day up to the twentieth week at which time the dosage was raised 5 mg. each week up to the thirty-sixth week and then discontinued. No particular restrictions of physical activities were enforced.

The routine of care in all our patients otherwise included the usual dietary vitamin and mineral supplement and rather frequent use of small doses of thyroid.

#### TOXIC EFFECTS

Outside of a rare report of mild nausea we have been unable to detect any ill-effect from the administration of diethylstilbestrol in pregnant women in dosages as high as 150 to 200 mg. daily. In no case was it necessary to reduce the dosage or stop the drug because of symptoms. On the contrary many patients reported a feeling of well-being and lessening of nausea and headache after beginning the drug. Congestion of the

All patients taking diethylstilbestrol were advised to reduce their salt intake and no increased edema was noted. Toxemia of pregnancy appeared in two patients, one being immediately after normal delivery of a living baby. The other toxemia patient was sectioned at six and one-half months and a living baby, which survived, was delivered.

TABLE III

Sterility Cases in Series	18	18.6%
Carried	16	88.8%
Aborted	2	11.2%
Deformed Babies	1	1.26%
Toxemia of Pregnancy	2	2.0%

#### DISCUSSION

We have presented a group of 96 patients with threatened and habitual abortion and threatened premature labor treated with diethylstilbestrol with more favorable results than we have been able to achieve with any other type of treatment. So far as we have observed the drug is without harm during pregnancy. It seems to us that its use is rational. There are however many questions which have not as yet been completely answered, such as:

1. Will diethylstilbestrol in large doses cause pituitary or other glandular imbalance which will become manifest later in life?
2. Is diethylstilbestrol in such large doses carcinogenic, and as such unsafe to give even to pregnant women?
3. Can diethylstilbestrol in any way affect the glandular balance of the child in utero, particularly the male child?

4. Is diethylstilbestrol the drug which will give better results in general use for the treatment of threatened or habitual abortion than drugs previously used?

In answer to the first three above questions we can only state that large doses of diethylstilbestrol have been administered to a large number of pregnant women (probably many thousands) for the past six to eight years and none of these ill-effects have been reported. Since it has been shown that the pregnant woman is at least 1000 times as tolerant of diethylstilbestrol as the nonpregnant one,<sup>44</sup> it may be that the dosages used in the preservation of pregnancy are relatively not large.

As to whether diethylstilbestrol is the drug which affords the pregnancy the most perfect endocrine sheltering or only a stepping stone to something better, only time will tell. In the meantime, in an analogous manner with vitamin B, which by virtue of its ability to reduce the insulin requirement of diabetics has become known as "Poor Man's Insulin," we like to think of diethylstilbestrol in pregnancy as "Poor Woman's Progesterone."

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#### DISCUSSION

DR. LEON KROHN (Los Angeles, by invitation): In considering the subject of threatened and habitual abortion, certain definite facts must be emphasized before entering into a theoretical and controversial endocrine discussion. Dr. Rosenblum has wisely pointed out some of these facts.

In a suspected case of threatened abortion, when the bleeding is painless it is important to do a speculum examination, as well as a gentle pelvic, since frequently a decidual polyp or severe erosion may be responsible for the bleeding.

It is also important, when evaluating results obtained in habitual abortion, that random and chance factors be excluded. Malpas, in a statistical study of 6,000 abortions, revealed the following enlightening information: if a patient had one spontaneous abortion, she has a 78 per cent chance of not repeating. If she has had two consecutive abortions she has a 62 per cent chance of not repeating. If she has three consecutive abortions she has only 27 per cent chance of carrying through to term. If she had four consecutive abortions, she has only six per cent chance of success.

Therefore, a patient should not be considered an habitual aborter unless she has had three consecutive abortions.

As early as 1933 my colleagues and I investigated the value of progesterone in the treatment of threatened and habitual abortion. In order to evaluate properly the encouraging clinical re-

sults obtained, we studied the effects of both progesterone and estrogenic hormone on human uterine motility, first in the puerperal and later in the nonpregnant uterus, by means of an intrauterine bag. Our results confirmed the animal experimental work of Knaus, Manzi, Reynolds and Allen, Hisaw and others, demonstrating that progesterone inhibits uterine motility. I would like to stress the fact that the progesterone we used at that time was not the synthetic material available now, but was prepared from fresh hog corpora lutea using the method of Corner and Allen. I am certain that this material was far more potent and effective in inhibiting uterine contractions than the synthetic material available today. Furthermore, I would like to emphasize the fact that aqueous corpus luteum extracts are probably physiologically inactive.

The most recent evidence that many threatened and habitual abortions are due to a deficiency of the corpus luteum hormone is furnished by pregnandiol studies. Pregnanediol is the biologically inactive steroid generally accepted to be the urinary excretion product of progesterone. Brown, Venning and Henry showed that in cases of threatened abortion, if the pregnandiol excretion persisted, there was a resumption of the normal course of pregnancy. Similar observations have been made by other investigators and more recently Guterman, using a more refined pregnandiol color test, was able to predict routinely the course of threatened abortion in 68 out of 73 cases (93 per cent).

When large amounts of progesterone are administered to men or women, either normal, hysterectomized and/or oophorectomized, pregnandiol appears in the urine. We observed in our studies, which were interrupted by the war, that by combining moderate doses of estrogenic hormone with progesterone, greater yields of urinary pregnandiol were obtained. This has been observed by Hamblen and other investigators and for this reason we have modified our treatment along the lines of Vaux and Rakoff by combining the ovarian hormones. Furthermore, it has been our custom for many years to treat prophylactically with estrogenic hormone, any early pregnancy existing in a patient who has been known to have had a hypoplastic uterus prior to conception.